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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,387	03/06/2002	Naoki Midoh	2002-0317A	2875

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WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,387	MIDOH ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15* is/are pending in the application.

4a) Of the above claim(s) *2-12* is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/04 has been entered.

[2] Claims 1-13 and 15 are pending in the application.

[3] Applicants' amendment to the claims, filed 12/23/2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Claims 2-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/18/2003.

[5] Claims 1, 13, and 15 are being examined on the merits.

[6] Applicants' arguments filed 12/23/2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim to Priority

[8] Applicants' claim for foreign priority under 35 USC § 119(a)-(d) to applications JP 11253040, filed 9/7/1999 and JP 2000104291, filed 4/6/2000, is acknowledged. Certified copies of the foreign priority documents have been filed in the instant application on 3/6/2002. English language translations of the foreign priority documents have been filed in the instant application on 6/21/2004 and 11/3/2004.

Information Disclosure Statement

[9] Information disclosure statements (IDSs) have been filed in the instant application on 3/6/2002 and 7/22/2003. The references cited in the IDSs have been considered by the examiner and copies of the IDSs were attached to the Office action mailed 1/21/2004.

[10] If the examiner has inadvertently overlooked an IDS that has previously been filed in the instant application, applicants' cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Sequence Compliance

[11] The instant application contains at least one nucleic acid and/or amino acid sequence that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicants have satisfied the requirements for sequence compliance, *i.e.,* the application contains a computer readable form (CRF) of the sequence listing, a paper copy thereof, a statement that the

CRF and paper copy of the sequence listing are identical, and, as the sequence listing is a substitute sequence listing, a statement that the paper copy of the substitute sequence listing contains no new matter. See papers filed 7/22/2002.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[12] The rejection of claims 13 and 15 under 35 U.S.C. 112, second paragraph, as set forth in the Office action mailed 7/23/2004 is withdrawn in view of the specifically recited hybridization conditions that are considered to be "stringent."

[13] Claim(s) 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The specification discloses, "[p]roduction of the cyclic depsipeptide synthetase ... depends on a media, culture conditions, or a host used" (p. 10, lines 19-21. In this case, it appears that the omitted step is culturing the host cell under conditions that are suitable for expression of the protein, particularly as the production of the protein is dependent upon media and culture conditions used to produce the protein.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] The rejection of claims 1 and 16-17 under 35 U.S.C. 112, first paragraph, as set forth in the Office action mailed 7/23/2004 is withdrawn in view of the amendment to the claims.

[15] The scope of enablement rejection of claims 13 and 15 under 35 U.S.C. 112, first paragraph, as set forth in the Office action mailed 7/23/2004 is maintained for the reasons of record and the reasons stated below. The specification, while being enabling for the polypeptide of SEQ ID NO:2 and a method for production thereof by culturing a host cell transformed with a vector comprising a nucleic acid encoding SEQ ID NO:2 under conditions suitable for production of the protein, does not reasonably provide enablement for the broad scope of polypeptides encompassed by claim 15, part (c) and methods for production thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are

summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: Claim 15 is so broad as to encompass a vast number of polypeptide variants of SEQ ID NO:2 having PF1022 synthetase activity. The polypeptide made by the method of claim 17 encompasses a vast number of polypeptide variants of SEQ ID NO:2 having PF1022 synthetase activity. While it is acknowledged the claimed or recited polypeptide variants are limited to those that are encoded by a nucleic acid that hybridizes to SEQ ID NO:1 under the recited hybridization conditions, this does not preclude the scope of claimed variants from encompassing polypeptide variants having one or more substitution(s), insertion(s), deletion(s), and addition(s) and any combination thereof within the limitation of the recited hybridization conditions. The enablement provided by the specification is not commensurate with the scope of the claims with regard to the extremely large number of polypeptide variants encompassed by the claims. In this case the disclosure is limited to SEQ ID NO:2 and a method of making SEQ ID NO:2.

(B) The nature of the invention; (C) The state of the prior art; and (D) The level of one of ordinary skill: The invention encompasses numerous variants of SEQ ID NO:2 having PF1022 synthetase activity and a method of making such variants. While other cyclic depsipeptide synthetases were known in the prior art at the time of the invention (see GenBank Accession Number S39842 in Appendix A), there was no disclosure of a polypeptide having PF1022 synthetase activity. As such, there was no disclosure in the prior art of mutants or variants of SEQ ID NO:2 having PF1022 synthetase activity such that one could compare sequences to determine regions of conservation where mutation(s) is/are likely to affect catalytic activity. Neither the specification nor the prior art at the time of the invention provides guidance for altering the polypeptide of SEQ ID NO:2 with an expectation of obtaining a polypeptide that has the desired alleged activity, *i.e.*, PF1022 synthetase activity. While methods of mutating a polypeptide were well advanced in the art at the time of the invention, it was not routine in the art for a skilled artisan to generate a vast number of variants of a novel polypeptide sequence to screen for and isolate by a trial and error process those variants having a desired activity/utility.

(E) The level of predictability in the art: The amino acid sequence of a polypeptide determines the protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which nucleotides in the encoding nucleic acid or amino acids in the encoded protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly

intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modification is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. As stated above, the state of the art at the time of the invention provides no guidance for altering the polypeptide of SEQ ID NO:2 with an expectation of obtaining a polypeptide that has the desired alleged activity/utility. The unpredictability of altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility is evidenced by Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York; cited in the Office action mailed 1/21/2004) which teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are supported by the references of Witkowski et al. (*Biochemistry* 38:11643-11650; cited in the Office action mailed 1/21/2004), Seffernick et al. (*J Bacteriol* 183:2405-2410), and Broun et al. (*Science* 282:1315-1317), which teach that minor alterations to a protein's sequence can have profound effects on the function of the protein. While it is

acknowledged that a single amino acid substitution in a protein is not likely to disrupt protein activity, the scope of variants is not limited to a single amino acid substitution, but encompasses additions, deletions, and insertions, and combinations of substitutions, additions, deletions, and insertions of a polypeptide that is 3,210 amino acids in length.

(F) The amount of direction provided by the inventor and (G) The existence of working examples: The specification provides only a single working example of the claimed polypeptide, *i.e.,* SEQ ID NO:2. The specification fails to disclose even a single working example of a variant of SEQ ID NO:2 with PF1022 synthetase activity. Other than the single working example of SEQ ID NO:2, the specification fails to provide any guidance as to the amino acids of SEQ ID NO:2 that can be altered by one or more substitution(s), addition(s), insertion(s), and/or deletion(s) and combinations thereof with an expectation of obtaining a polypeptide having the desired activity/utility. While the examiner acknowledges that "the absence of working examples will not by itself render the invention non-enabled," it is noted that "[l]ack of a working example...is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." See MPEP § 2164.02. In this case, the art is highly unpredictable as noted above and the absence of a working example of a variant of SEQ ID NO:2 having PF1022 synthetase activity is a factor to be considered in the instant rejection.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a given polypeptide were known in the art at the time of the invention, *e.g.,* site-directed

mutagenesis, it was not routine in the art to screen for *all* polypeptides having a substantial number of substitutions or modifications as encompassed by the claims and to screen and isolate those by a trial and error process for those variants having the desired activity/utility. In view of the lack of guidance and working examples, a skilled artisan must replace each of the 3,210 amino acids of SEQ ID NO:2 with 19 other common amino acids just for single amino acid substitutions at all 3,210 amino acids of SEQ ID NO:2. Take into consideration that one must perform not only single amino acid substitutions, but also single amino acid additions, deletions, and insertions, multiple amino acid substitutions, additions, deletions, and insertions, and combinations thereof within the limit of the hybridization conditions to make the full scope of claimed or recited variants of SEQ ID NO:2. One must next screen all variants for those that have PF1022 synthetase activity. Such experimentation is not considered to be routine in the art.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the

experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: Applicants argue the scope of enablement rejection is overcome by amending the claims to recite specific hybridization language. Applicants assert claims 13 and 15 were amended to recite "the specific stringent hybridization conditions disclosed in the specification as suggested by the Examiner during the interview on October 19, 2004."

Applicants' argument is not found persuasive. In response to applicants' assertion that the examiner suggested recitation of hybridization conditions to overcome a scope of enablement rejection, it is noted that the examiner can find no suggestion of such an amendment in the written record.

In this case, while the claims are further limiting in the scope of variants that are encompassed by parts (c) of claims 13 and 15 filed 6/21/2004, the recitation of polypeptides sharing a % identity with SEQ ID NO:2 or polypeptides encoded by a nucleic acid that hybridizes with SEQ ID NO:1 still encompass variants of SEQ ID NO:2. The recitation of hybridization language does not by itself remedy the deficiencies of the specification in guiding a skilled artisan in making the full scope of claimed variants. As such, it is the examiner's position that, even in view of the amendment to replace a "% identity" limitation with a "hybridization" limitation, undue experimentation is required for a skilled artisan to make the full scope of the claimed invention.

Applicants argue it would only require routine experimentation for a skilled artisan to isolate DNA that hybridizes under the recited conditions to SEQ ID NO:1 to produce a protein having the recited activity.

Applicants' argument is not found persuasive. At least for the reasons of record and those stated above, it is the examiner's position that undue experimentation is required for a skilled artisan to make the full scope of claimed polypeptides.

Claim Rejections - 35 USC § 102

[16] The rejection of claim(s) 1 and 15 under 35 U.S.C. 102(a) as being anticipated by Weckwerth et al. as set forth in the Office action mailed 7/23/2004 is withdrawn in view of applicants' submission of an English language translation of JP 11253040. As applicants have perfected a claim for foreign priority under 35 USC § 119(a)-(d) to JP 11253040, the reference of Weckwerth et al. is no longer available as prior art under 35 U.S.C. 102(a).

Claim Rejections - 35 USC § 103

[17] The rejection of claim(s) 13 under 35 U.S.C. 103(a) as being unpatentable over Weckwerth et al. in view of Leitner et al., Matsudaira, Wozney, and Aoyagi et al. as set forth in the Office action mailed 7/23/2004 is withdrawn in view of applicants' submission of an English language translation of JP 11253040.

Conclusion

[18] Status of the claims:

- Claims 1-13 and 15 are pending.
- Claims 2-12 are withdrawn from consideration.
- Claim 1 appears to be in a condition for allowance.
- Claims 13 and 15 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday and alternatve Fridays from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

03-03-05
DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER